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Received: 9 November 2017 | Revised: 19 February 2018 | Accepted: 3 May 2018

DOI: 10.1002/ijgo.12521

REVIEW ARTICLE

Gynecology

WILEY | International Journal of Gynecology & Obstetrics FIGO

An evidence-based approach to assessing surgical versus clinical diagnosis of symptomatic endometriosis

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Funding Information
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Abstract

Challenges intrinsic to the accurate diagnosis of endometriosis contribute to an extended delay between the onset of symptoms and clinical confirmation. Intraoperative visualization, preferably with histologic verification, is considered by many professional organizations to be the gold standard by which endometriosis is diagnosed. Clinical diagnosis of symptomatic endometriosis via patient history, physical examination, and noninvasive tests, though more easily executed, is generally viewed as less accurate than surgical diagnosis. Technological advances and increased understanding of the pathophysiology of endometriosis warrant continuing reevaluation of the standard method for diagnosing symptomatic disease. A review of the published literature was therefore performed with the goal of comparing the accuracy of clinical diagnostic measures with that of surgical diagnosis. The current body of evidence suggests that clinical diagnosis of symptomatic endometriosis is more reliable than previously recognized and that surgical diagnosis has limitations that could be underappreciated. Regardless of the methodology used, women with suspected symptomatic endometriosis would be well served by a diagnostic paradigm that is reliable, conveys minimal risk of under- or over-diagnosis, lessens the time from symptom development to diagnosis, and guides the appropriate use of medical and surgical management strategies.

KEYWORDS

Diagnosis; Endometriosis; Histology; Infertility; Laparoscopy; Pelvic examination; Pelvic pain; Surgery

1 | INTRODUCTION

Endometriosis is a common gynecologic condition that affects approximately 6%–10% of reproductive-aged women.[1] Pain, a frequent symptom of endometriosis that manifests as dysmenorrhea, chronic pelvic pain, dyspareunia, and/or dyschezia, can be debilitating. Even among women without extensive disease, pain can limit daily life activities and negatively affect health-related quality of life and

productivity, with substantial economic consequences.[2,3] The other major sequela of endometriosis is infertility that, for some women, is the only indicator of the disease. Endometriosis is detected among approximately 20%–50% of women who undergo treatment for infertility and who do not present with symptoms such as pain or menstrual irregularities.[1]

The profound influence of untreated endometriosis on many aspects of women's lives underscores the need for timely diagnosis and initiation of treatment. Nonetheless, diagnostic challenges coupled with the requirement for surgical intervention to make a diagnosis often result in considerable delay to clinical management of affected individuals. Studies that have evaluated the timing of diagnosis in various parts of the world have consistently reported a mean or median interval of at least 7 years from the time a patient first experiences symptoms of endometriosis until she receives a confirmed diagnosis.[2,4,5] In the interim, many women with endometriosis undergo consultations with multiple practitioners and receive misdiagnoses (e.g. chronic pelvic pain syndrome, idiopathic sterility, or pelvic inflammatory disease) before finally reaching the correct diagnosis.[4]

The best methods to diagnose endometriosis and to determine the extent and pathologic severity of this disease are subject to debate.[1] Visualization—typically by laparoscopy with histologic confirmation—is generally considered to be the gold standard (Table 1).[1,6–9] However, this technique is not without its limitations, costs, and risks.[7,8] In practice, clinicians often rely on medical history, presenting symptoms, and findings on physical examination (i.e. a clinical diagnosis), with or without imaging studies, as the basis for initiating therapy. This practice is consistent with guidance from the American College of Obstetricians and Gynecologists,[1] the Society of Obstetricians and Gynaecologists of Canada,[7] the European Society of Human Reproduction and Embryology[8] (also endorsed by the Royal College of Obstetricians and Gynaecologists), and the World Endometriosis Society (WES).[9] These organizations advocate for empiric treatment before laparoscopy in selected patients (Table 1).[1,7–9] The American Society for Reproductive Medicine (ASRM) guidelines state that laparoscopy before empiric treatment is the "preferred approach, although further studies are warranted" (Table 1).[6] These guidelines are predicated on the assumption that isolated clinical diagnosis is of limited accuracy. Nonetheless, as understanding of endometriosis increases and improved noninvasive methods for its detection are developed, reevaluation of clinical diagnosis as a viable, practical, reliable, and widely accessible alternative to surgical diagnosis merits consideration.

In response to the ongoing question of clinical versus surgical diagnosis for endometriosis, we have undertaken a critical evaluation of the accuracy of both approaches. Relevant published data were identified by searching the MEDLINE database for studies that described correlations between the presence of endometriosis and symptoms, physical findings, imaging studies, or surgical and/or histologic findings. Given the limited information available on endometriosis within the adolescent population, our discussion will focus on endometriosis among adults, unless otherwise indicated.

2 | ENDOMETRIOSIS DEFINITION AND STAGING

Any discussion of the diagnosis of endometriosis must begin by defining what constitutes this disease. Endometriosis is traditionally defined by the presence of lesions, which vary considerably in appearance, size, and location, and are histologically confirmed by the detection of endometrial glands, endometrial stroma, and/or hemosiderin-laden macrophages. However, an internationally accepted definition proposed in 2017 describes endometriosis as "a disease characterized by the presence of endometrium-like epithelium and stroma outside the endometrium and myometrium. Intrapelvic endometriosis can be located superficially on the peritoneum (peritoneal endometriosis), can extend 5 mm or more beneath the peritoneum (deep endometriosis), or can be present as an ovarian endometriotic cyst (endometrioma)".[10] These definitions are based solely on pathology and do not consider symptoms such as pain and infertility that act as drivers for the initiation of treatment. The ability to diagnose endometriosis clinically requires a different approach in which symptoms are considered to be paramount and histology is a secondary criterion. This paradigm would not require imaging or laparoscopy for diagnosis unless clinically indicated; for example, in the presence of a mass or findings suspicious for malignancy.

Ambiguity is also found in the staging of endometriosis. A broadly applicable and prognostically relevant classification system for endometriosis has yet to be established.[11] Among the available options, the revised ASRM (rASRM) classification and staging system[12] is the most frequently used in both research and clinical practice.[13] The rASRM system uses laparoscopic findings to subdivide endometriosis severity into four stages: I (minimal), II (mild), III (moderate), and IV (severe).[12] However, the stage of endometriosis does not necessarily correlate with the severity of pain that the patient experiences, the risk of infertility, or other outcomes that are important to patients and their clinicians.[11,14] The disconnect between rASRM stage and pain is not unexpected; the scale used to derive this classification system had been designed to predict the efficacy of conservative surgical treatment to improve fertility and did not include pain as an outcome variable.[15] Indeed, women with disease categorized as stage I or II can experience considerable pain, infertility, or other endometriosis-related symptoms, whereas severe disease has been detected among asymptomatic women who undergo laparoscopy for other indications.[16]

The use of "asymptomatic" in the context of endometriosis refers to the presence of endometrial lesions without associated pain, infertility, ovarian masses, or dysfunction of the bladder or bowel. Although the rASRM classification has the advantages of being simple to use and easy for patients to understand, the caveats discussed above, as well as its lack of utility in the classification of deep endometriosis, make it less than ideal. A newer concept is to categorize endometriosis by its presentation: superficial, ovarian endometrioma, or deep disease. Associations have been made between symptom presentation and endometriosis stratified into these three categories (discussed below in Section 3).[17,18]

TABLE 1 Summary of key recommendations regarding the diagnosis and treatment of endometriosis.

Method of diagnosis	ACOG[1]	ASRM[6]	SOGC[7]	ESHRE[8]	WES[9]
Clinical	Definitive diagnosis can only be made by surgery with histologic verification	Laparoscopy before empiric treatment is the "preferred approach, although further studies are warranted"	"Investigation of suspected endometriosis should include patient history, physical examination, and imaging studies"	"The diagnosis of endometriosis is suspected based on the history, the symptoms and signs, is corroborated by physical examination and imaging techniques and is finally proven by histological examination of specimens collected during laparoscopy"	Diagnostic gold standard is laparoscopic visualization, preferably with histologic confirmation
	Empiric treatment can be offered before diagnostic laparoscopy, although a response to therapy does not confirm the diagnosis	Operative visualization can be an acceptable surrogate to histologic diagnosis in some cases, although atypical lesions are difficult to characterize without biopsy	Direct visualization at laparoscopy with histologic verification is the gold standard; however, empiric treatment can be offered before diagnostic laparoscopy	Empiric treatment for pain can be offered before diagnostic laparoscopy	Empiric medical therapy can be initiated before surgical diagnosis and treatment, but should be preceded by a full evaluation
TVUS	Preferred imaging technique when assessing endometriosis and/or deep endometriosis of the rectum or rectovaginal septum	Imaging modalities have not been found to increase diagnostic accuracy	"First-line investigational tool for suspected endometriosis"	"Useful for identifying or ruling out rectal endometriosis" Recommended to diagnose or exclude ovarian endometrioma	Not discussed
MRI	Reserved for suspected rectovaginal or bladder endometriosis when ultrasonographic results are equivocal	Imaging modalities have not been found to increase diagnostic accuracy	Could be required if deep endometriosis is suspected	Usefulness for diagnosing peritoneal endometriosis is not well-established	Not discussed

Abbreviations: ACOG, American College of Obstetricians and Gynecologists; ASRM, American Society for Reproductive Medicine; SOGC, Society of Obstetricians and Gynaecologists of Canada; ESHRE, European Society of Human Reproduction and Embryology; WES, World Endometriosis Society; TVUS, transvaginal ultrasonography; MRI, magnetic resonance imaging.

Given the limitations of individual staging systems, the 2017 WES consensus statement recommends the use of a "classification toolbox" that includes the rASRM system as well as the Enzian and the Endometriosis Fertility Index classification systems.[11,19] The WES consensus statement further advocates taking steps to improve the classification of endometriosis, particularly for cases where surgery is not performed.

3 | CLINICAL DIAGNOSIS OF ENDOMETRIOSIS

Clinical presentations of endometriosis are highly diverse; none of the presenting signs or symptoms are pathognomonic for this disease. Because of the overlap in symptoms with other gynecologic conditions (e.g., primary dysmenorrhea, adenomyosis, pelvic adhesions, ovarian cysts, pelvic inflammatory disease)[7] and chronic pain syndromes (e.g., irritable bowel, interstitial cystitis/painful bladder, fibromyalgia, musculoskeletal disorders),[6] differential diagnosis is an important facet of identifying endometriosis. By way of example, gynecologic conditions such as primary dysmenorrhea, adenomyosis, pelvic adhesions, ovarian cysts, and pelvic inflammatory disease should be excluded, as should chronic pain syndromes, including irritable bowel, interstitial cystitis, painful bladder, fibromyalgia, and musculoskeletal disorders. Patient and family history, assessment of pain characteristics, and identification of menstrual irregularities can be informative for ruling out other causes of pelvic pain. Individual symptoms may be informative in terms of assessing the likelihood that a patient has endometriosis but cannot, in and of themselves, rule endometriosis in or out.

3.1 | Discriminatory value of pelvic pain

Pelvic pain is a common occurrence among the general population.[20] Although pain is a cardinal symptom of endometriosis, discerning whether it can be attributed to endometriosis is challenging. Pelvic pain among women can arise from a variety of sources and have multiple presentations and characteristics, which complicates its value as a marker of endometriosis. As shown in Table 2, dysmenorrhea, chronic pelvic pain, chronic nonmenstrual pelvic pain, and dyspareunia are the most consistently reported types of pain among women with endometriosis.[14,21–30] Overall, dysmenorrhea is the most frequent pain symptom, reported by the majority of women who have proven endometriosis. Chronic pelvic pain and/or chronic nonmenstrual pelvic pain are generally less common than dysmenorrhea, but are notable for their higher occurrence rates in women with proven or self-reported endometriosis than in women without endometriosis.[14,21,24,25,28]

The temporal relationship between pain and the menstrual cycle can help to distinguish between primary and secondary dysmenorrhea, the latter being a catch-all category for pain caused by disorders of the reproductive organs such as endometriosis. Pelvic pain associated with primary dysmenorrhea typically occurs with the onset of menstrual flow and lasts for approximately 8–72 hours.[31] By contrast, endometriosis pain is progressive, can be cyclic or acyclic, and could extend beyond the 3-day early follicular-phase timeframe associated with primary dysmenorrhea. In addition, primary dysmenorrhea can be differentiated from secondary dysmenorrhea by its rapid response to analgesia with nonsteroidal anti-inflammatory drugs (NSAIDs), as well as the non-progressive persistent severity of the pain and continued response to treatment with NSAIDs.[6]

Attempts to detect correlations between the severity of disease (as defined by the volume, location, or type of endometriotic lesions) and the prevalence or severity of pain have produced disparate results.[21,26,27,29] Although a study by Ashrafi et al.[21] found an increased proportion of patients who reported dysmenorrhea, pelvic pain, and/or dyspareunia among those with stage III–IV versus stage I–II disease, other investigators have not observed such a correlation.[14,26,27] However, it is important to note that the population studied by Ashrafi et al.[21] comprised infertile women, who could be a physiologically different group than women with endometriosis who have never experienced infertility. As mentioned above in Section 2, the rASRM classification of endometriosis staging was not designed to reflect the degree of pain that a patient might be experiencing.

The data are also inconsistent regarding a link between location of endometriosis and pain characteristics.[14,27,28] However, there does seem to be an association between the type of endometriosis and pain features. Among the three types of endometriosis (superficial peritoneal lesions, ovarian endometrioma, and deep endometriosis), the presence of deep endometriosis has been most consistently linked to chronic pelvic pain.[18] By contrast, superficial lesions are less frequently associated with pain and often observed among asymptomatic women.[17] The presence of ovarian endometriomas does not correlate with dysmenorrhea severity, and dysmenorrhea is less commonly associated with isolated ovarian endometriomas compared with other disease manifestations.[18]

The available evidence confirms that women with endometriosis typically experience pain. Although the occurrence of pelvic pain alone is insufficient to diagnose endometriosis or to categorize the type or stage of disease, certain characteristics (e.g. dysmenorrhea, progression, and insufficient response to NSAIDs or oral contraceptives) are indicative of endometriosis. It is important to note that the prevalence of endometriosis in asymptomatic women is not known. Reports of endometriosis observed at the time of laparoscopic tubal ligation in asymptomatic women are limited, and what reports are available likely underestimate disease burden because the thoroughness of peritoneal surface examination is typically much greater in symptomatic versus asymptomatic women.

3.2 | Infertility as an indicator of endometriosis

Infertility is considerably more common among women with endometriosis than among individuals without this condition. In a UK case–control study, women diagnosed with endometriosis were greater than six times more likely to have a history of infertility than were women without endometriosis.[24] Given this association, endometriosis should be considered as a possible cause of, or comorbidity among, women with infertility, particularly those who demonstrate

TABLE 2 Common pain symptoms among women with endometriosis.[a]

Study (no. of patients)	Population	Patients		
		Dysmenorrhea	CPP[b]	Dyspareunia
Ashrafi et al. 2016[21] (n=673)	Infertile women with laparoscopically diagnosed endometriosis	54–81[c]	31–52[c]	29–55[c]
	Infertile women with no evidence of endometriosis on laparoscopy	41	19	20
Apostolopoulos et al. 2016[22] (n=96)	Women with laparoscopically diagnosed endometriosis but without histologic confirmation	67–89[c]	59–67[c]	24–41[c]
Schliep et al. 2015[14] (n=326)	Women with laparoscopically diagnosed endometriosis	38–91	44	14–55
	Women with a laparoscopically normal pelvis	38–79	30	9–32
Bellelis et al. 2010[23] (n=892)	Women with histologically confirmed endometriosis	28[d]	57	55
Ballard et al. 2008[24] (n=5540)	Women with a diagnosis of endometriosis	25[e]	16[e]	9[e]
	Matched control individuals	3[e]	2[e]	1[e]
Flores et al. 2008[25] (n=1285)	Women with self-reported endometriosis	83	80	52
	Women who did not self-report endometriosis	59	23	20
Vercellini et al. 2007[26] (n=1054)	Consecutive women with endometriosis undergoing first-line conservative or definitive surgery	57[f]	30[f]	21[f]
GISE 2001[27] (n=469)	Consecutive women with pain symptoms lasting ≥6 mo and laparoscopic evidence of endometriosis affecting the stated anatomic sites	O: 77	O: 62	O: 39
		P: 88	P: 57	P: 51
		O&P: 92	O&P: 68	O&P: 51
		RVS: 100	RVS: 67	RVS: 80
Eskenazi et al. 2001[28] (n=90)	Women with surgically confirmed endometriosis	65	32	22
	Women with no evidence of endometriosis on laparoscopy or laparotomy	30	15	23
Porpora et al. 1999 [29] (n=90)	Consecutive women with histologically confirmed endometriosis	66 [f]	49 [f]	38 [f]
Forman et al. 1993[30] (n=99)	Infertile women with laparoscopically diagnosed endometriosis	53	20	23
	Infertile women without endometriosis	28	18	25

Abbreviations: CPP, chronic pelvic pain; GISE, Gruppo Italiano per lo Studio dell'Endometriosi; O, ovary; P, peritoneum; O&P, ovary and peritoneum; RVS, rectovaginal septum.
[a]Values are given as percentages.
[b]Includes chronic pelvic pain and chronic nonmenstrual pelvic pain.
[c]Percentage varies depending on the disease stage.
[d]Percentage of patients experiencing incapacitating dysmenorrhea.
[e]Reflects the prevalence of symptoms recorded in patient medical records.
[f]Percentage of patients experiencing moderate or severe pain symptoms.

other symptoms consistent with endometriosis. Pain, menstrual irregularities, and fatigue (symptoms that are generally associated with endometriosis) have been shown to be more prevalent among infertile women with endometriosis compared with infertile women without endometriosis.[21]

3.3 | Other symptomatic indicators of endometriosis

Studies evaluating risk factors or characteristics associated with endometriosis have reported linkage with longer duration of menses, shorter menstrual cycle length, increased menstrual volume, irregular menstrual periods, post-coital bleeding, and dyschezia,[21,24,25,32] although the findings are not consistent. Whereas no single characteristic may reach significance as a prognostic factor on a population level, a constellation of endometriosis-related symptoms can be a strong indicator of disease. Indeed, Ballard et al.[24] found that the likelihood of endometriosis increased with the number of symptoms present, with elevations in relative risk ranging from five-fold for one symptom to 85-fold when seven or more symptoms were present.

3.4 | Accuracy of physical examination as a diagnostic tool

Multiple studies have sought to quantify the ability of a physical examination to detect endometriosis by gauging its accuracy relative to surgical diagnosis (Table 3).[28,33–37] Patient selection and examination methods differ among individual studies, which confound the overall estimation of accuracy. These limitations notwithstanding, the specificity (percentage of all patients without surgically confirmed endometriosis who have a negative clinical diagnosis), positive predictive value (PPV; percentage of all patients with clinically diagnosed endometriosis that is surgically verified), and negative predictive value (NPV; percentage of all patients without clinically diagnosed

TABLE 3 Accuracy of physical examination in diagnosing endometriosis for patients who underwent laparoscopy.[a]

Study (no. of patients)	Definition of positive physical examination	Anatomic site	Sensitivity	Specificity	PPV	NPV
Hudelist et al. 2011[33] (n=129)	"Palpable nodule or thickened area or a palpable cystic expansion with topographic-anatomical correlation"	Ovary	41	99	92	87
		Rectum and/or sigmoid	39	97	86	84
		USL	50	80	43	84
		Pouch of Douglas	76	92	64	95
		Vagina	73	98	80	97
		RVS	78	98	78	98
		Bladder	25	100	100	98
Hudelist et al. 2009[34] (n=200)	"Palpable nodularity or stiffened and/or thickened area or a palpable cystic expansion with topographic-anatomical correlation"	Right/left ovary	38/23	99/99	90/75	92/90
		Right/left USL	52/74	97/89	67/65	94/93
		Pouch of Douglas	70	98	84	95
		Vagina	64	100	100	96
		RVS	88	99	78	99
		Bladder	25	100	100	98
		Rectum	46	99	96	85
Bazot et al. 2009[35] (n=92)[b]	Lesions visualized on posterior vaginal fornix; infiltration and/or nodule involving the vagina, torus uterinus, USL, or pouch of Douglas; or infiltration and/or mass involving the rectosigmoid colon	USL	74	78	97	24
		Vagina	50	87	65	78
		RVS	18	96	40	90
		Intestine	46	72	78	38
Abrao et al. 2007[36] (n=104)[b]	Nodule of RVS; thickening or nodule in the USL or cul-de-sac	Rectosigmoid	72	54	63	64
		Retrocervical	68	46	45	69
Cheewadhanaraks et al. 2004[37] (n=116)	Tenderness and/or nodularity of the cul-de-sac or USL	Cul-de-sac and/or USL	NA	NA	86–95[c]	NA
Eskenazi et al. 2001[28] (n=90)	USL scarring, nodularity or pain; pouch of Douglas nodularity or pain; vaginal lesions; painful or fixed adnexal masses; or fixed uterus and/or pain on movement of uterus	Any	76	74	67	81

Abbreviations: PPV, positive predictive value; NPV, negative predictive value; USL, uterosacral ligament; RVS, rectovaginal septum; NA, not applicable.
[a]Values are given as percentages.
[b]Data are for a diagnosis of deep endometriosis.
[c]Values varied depending on the measure used (i.e. tenderness, nodularity, or tenderness plus nodularity).

endometriosis who are also surgically negative) of a physical examination are generally high (80%–100%), particularly among women with a strong pretest likelihood of disease based on symptoms. Sensitivity of physical examination (i.e. percentage of patients with clinically diagnosed endometriosis who have a positive surgical result) shows a greater dependence on location of the lesion than do other measures of diagnostic accuracy.[33–35] This phenomenon is not unexpected, given that the ease of detecting lesions by physical examination varies by their location. The lower values for sensitivity (18%–88%) when compared with specificity (46%–100%) or PPV (40%–100%) suggest that false-negative physical examination findings occur more frequently than do false-positive findings.

4 | IMAGING STUDIES AS AN ADJUNCT TO CLINICAL DIAGNOSIS

The data described above in Section 3.4 and presented in Table 3 reflect the results of physical examination alone, without the inclusion of other measures of disease detection (other than historical symptoms consistent with endometriosis). In addition, they do not include imaging results, which have increasingly become an integral component of the diagnostic process among patients with suspected endometriosis.

4.1 | Ultrasonography

Imaging methods such as ultrasonography have inherent value for their ability to identify causes of abdominal pain and menstrual symptoms other than endometriosis (e.g. adenomyosis). In the context of endometriosis, the addition of transvaginal ultrasonography (TVUS) to pelvic examination increases the accuracy of a clinical diagnosis of adnexal and rectal disease.[34] Hudelist et al.[34] reported almost universal increases in the sensitivity of endometriosis detection when TVUS was combined with pelvic examination versus pelvic examination alone among women with symptoms suggestive of endometriosis. Of note, sensitivity for detecting ovarian endometriosis increased from approximately 30% with pelvic examination alone to greater than 96%

with pelvic examination plus TVUS. Moreover, endometriosis of the urinary bladder, which was detected in one of four patients via physical examination, was identified in three of four patients with the addition of TVUS.[34]

A strong correlation has been observed between TVUS markers and laparoscopic findings. Among 120 consecutive women with chronic pelvic pain evaluated by Okaro et al.,[38] "hard markers" on TVUS (structural abnormalities such as endometriomas or hydrosalpinges) demonstrated a 100% correlation (24 of 24 women) with laparoscopic findings. In addition, "soft" markers (e.g. reduced ovarian mobility, site-specific pelvic tenderness, and the presence of loculated peritoneal fluid in the pelvis) were predictive of pelvic pathology, with 37 of 51 (73%) of women with only soft markers by TVUS having a true-positive result. These data lend support to an empiric course of treatment, as 61 of 75 (81%) women evaluated by TVUS had their need for treatment confirmed laparoscopically.

TVUS is generally considered the first-line imaging approach for evaluating suspected endometriosis. Professional society guidelines cite its utility for detecting endometriosis and/or deep endometriosis of the rectum or rectovaginal septum, and in diagnosing or excluding ovarian endometrioma (Table 1).[1,8] Recent evidence suggests that the diagnostic acumen of TVUS for deep endometriosis of the bowel may be increased by adding bowel preparation.[39] However, the effectiveness of TVUS in detecting superficial peritoneal disease is extremely limited. This method could, therefore, be of reduced value for adolescents as superficial lesions are the predominant form of endometriosis in this population.[40]

4.2 | Magnetic resonance imaging

Owing to its higher costs relative to other imaging modalities, magnetic resonance imaging (MRI) is less frequently applied for the assessment of endometriosis. However, MRI is useful in cases where ultrasonography findings are equivocal[1,7] and in carefully selected, high-risk patients (e.g., those with extensive pelvic adhesions of suspected ureteral involvement).[41] Nonetheless, this method is helpful for cases where ultrasonographic findings are equivocal[1,7] or for use among carefully selected high-risk patients such as those with extensive pelvic adhesions or suspected ureteral involvement.[41] One advantage of MRI is that interpretation of the results is less operator-dependent compared with TVUS.[42] As shown in Table 1, the American College of Obstetricians and Gynecologists[1] and the Society of Obstetricians and Gynaecologists of Canada[7] guidelines support selective use of MRI for cases where ultrasonographic results are not clear regarding rectovaginal or bladder endometriosis[1] and if deep endometriosis is suspected.[7]

4.3 | Recommendations for imaging

Recommendations for the use of imaging modalities differ considerably among professional society guidelines and consensus statements (Table 1). The recommendations provided reflect the available evidence at the time when each document was developed, the expert opinions of the writing committee members, and the questions that these committees were seeking to answer. Hence, such differences are not unexpected. As the evidence base for imaging modalities in the diagnosis of endometriosis grows, it is likely that increased uniformity and strength of imaging recommendations will emerge.

Estimates of the accuracy of physical examination, with or without imaging, for identifying endometriosis must include the caveat that these tools are compared with laparoscopic visualization, which has its own limitations (see Section 5 below). It is also worth noting that the studies described herein have not quantified the accuracy of a comprehensive approach to diagnosis that incorporates patient history, pain features, response to NSAIDs or oral contraceptives, characteristics of the menstrual cycle, physical examination findings, and imaging studies. With all these facets of disease considered in totality, a more precise clinical picture is likely to emerge. Studies of combinations of two or three noninvasive tests (often involving a biomarker) have yet to meet the criteria for a replacement test for diagnostic surgery, according to a recent systematic review.[43] However, using a combination of symptoms, clinical factors, and patient characteristics, Nnoaham et al.[32] created models that had reasonable accuracy for predicting stage III and IV disease (yet lacked discriminatory power to detect stage I or II disease). Regardless, the true value of a clinical diagnosis might not rest solely on its accuracy versus surgical diagnosis, but rather in its broad application and ability to allow for early initiation of treatment.

5 | SURGICAL DIAGNOSIS OF ENDOMETRIOSIS

Laparoscopic visualization is the current standard for diagnosis of endometriosis.[1,7,8] Reliance on this method for endometriosis detection in symptomatic women is predicated on preoperative selection of women with a high pretest likelihood of endometriosis and on visual recognition by the surgeon of a full range of potential endometriosis lesions. Notably, endometriosis is not detected among one-quarter of women who undergo a laparoscopic procedure for chronic pelvic pain and/or suspected endometriosis.[44–46] Superficial endometriosis lesions present a particular diagnostic dilemma for physicians owing to their heterogeneous visual appearance and the fact that nonpigmented peritoneal lesions often represent highly active endometriotic implants.[47] Visual identification is compromised by the myriad phenotypic appearances and pathologic characteristics (e.g., endosalpingiosis, mesothelial hyperplasia, hemosiderin deposition, hemangiomas, carbon from previous laser treatments) of lesions that can be confused with endometriotic implants. In addition, endometriosis, as defined by the histologic identification of stroma and glands, may be present in normal-appearing tissue.[17] Such is the case for microscopic lesions that reside in visually normal peritoneum.

A definitive diagnosis of endometriosis has traditionally required histologic confirmation of disease after visualization of lesions. Standard histologic criteria include the presence of at least two of the following: endometrial glands, endometrial stroma, and hemosiderin-laden macrophages. These criteria were established before appreciation of the prevalence of non-blue and/or black lesions and without

understanding of the natural history of superficial peritoneal endometriosis lesions. As shown in Table 4, a survey of studies that evaluated the accuracy of laparoscopic identification reveals that as many as 67% of lesions considered to be endometriosis on visual inspection were not confirmed histologically.[44–46,48–52] The potential for false positives was generally higher at stages I and II in comparison with III and IV, although there is an apparent decrease in PPV between stages III and IV.

Location also influences the diagnostic accuracy of laparoscopic visualization when histology is considered as the gold standard. For example, Albee et al.[50] evaluated laparoscopic visualization of endometriosis among 512 women with pelvic pain. These investigators found that the accuracy was less than 70% for lesions located on the pelvic sidewall, uterosacral ligament, and bladder. The NPVs for these locations were 39%–56%, suggesting a high degree of false-negative results; these cases tended to be atypical lesions with endometriosis (defined by the presence of both endometrial glands and stroma) identified only by histology. However, with carefully conducted biopsy procedures and selected portions of specimens sent for pathologic examination, endometriosis is detected in at least 75% of biopsies. Whether biopsy is routinely performed and this high confirmation rate is achieved in clinical practice remains to be determined.

Comparisons among studies also reveal considerable heterogeneity in the sensitivity, specificity, PPV, and NPV of laparoscopic diagnosis of endometriosis (Table 4), which may be due, at least in part, to interobserver variability. This phenomenon can compromise accurate diagnosis of endometriosis by laparoscopy.[44] Differences in lesion interpretation and staging can occur among laparoscopists and/or pathologists evaluating biopsy results. Interestingly, a study that evaluated inter-rater agreement on endometriosis diagnosis and staging found that surgeons and expert reviewers demonstrated

TABLE 4 Accuracy of laparoscopic visualization for diagnosis of endometriosis.[a,b]

Study (no. of patients)	Population	Stage	Sensitivity	Specificity	PPV	NPV
Fernando et al. 2013[44] (n=431)	Women who underwent laparoscopic biopsy for suspected endometriosis	All	NA	NA	75	NA
		I	NA	NA	50	NA
		II	NA	NA	80	NA
		III	NA	NA	78	NA
		IV	NA	NA	79	NA
Stegmann et al. 2008[45] (n=133)	Women who underwent laparoscopic biopsy for chronic pelvic pain	All	98	21	64	88
Kazanegra et al. 2008[46] (n=104)	Women who underwent laparoscopic biopsy for suspected endometriosis	All	NA	NA	87	NA
		I	NA	NA	76	NA
		II	NA	NA	90	NA
		III	NA	NA	100	NA
		IV	NA	NA	91	NA
El Bishry et al. 2008[48] (n=48)	Women who underwent laparoscopic biopsy for pelvic pain	All	NA	NA	75	NA
		I	NA	NA	33	NA
		II	NA	NA	71	NA
		III	NA	NA	92	NA
		IV	NA	NA	73	NA
Almeida Filho et al. 2008[49] (n=976)	Women who underwent laparoscopic biopsy for pelvic pain and/or infertility	All	98	79	72	98
Albee et al. 2008[50] (n=512)	Women who underwent laparoscopic biopsy for pelvic pain	All	62–100[b]	40–83[c]	71–94[c]	26–100[c]
Stratton et al. 2003[51] (n=48)	Women who underwent laparoscopic biopsy for pelvic pain	All	NA	NA	86	NA
		I	NA	NA	62	NA
		II	NA	NA	100	NA
		III	NA	NA	100	NA
		IV	NA	NA	86	NA
Walter et al. 2001[52] (n=44)	Women who underwent laparoscopic biopsy for chronic pelvic pain	All	97	77	45	99

Abbreviations: PPV, positive predictive value; NPV, negative predictive value; NA, not applicable.

[a]Values are given as percentage.

[b]Endometriosis was confirmed by histologic evidence of both endometrial glands and stroma for all studies except Almeida Filho et al. [49] (in which the presence of glands and stroma was not specified) and Stratton et al. [51] (in which the presence of endometrial glands or stroma was required).

[c]Ranges reflect differences depending on the anatomic location of the lesion.

high levels of agreement when viewing digital images of laparoscopic findings or operative reports.[53] However, agreement decreased considerably after viewing histologic findings. These results highlight potential differences in interpretation among laparoscopists and pathologists that are further obscured by ambiguities and differences in the available staging systems.

Laparoscopic surgery, with or without lesion biopsy for histologic confirmation, is intrinsically associated with an increased risk of intraoperative injury such as vascular injury, bowel or bladder perforation, and damage to the ureter.[7,8] Complications of anesthesia can also occur. Major or minor adverse events arising from laparoscopy are found in an estimated 8.9% of all procedures.[54] Even though this rate represents the minority of cases, it should be factored into the risk-to-benefit equation and weighed against the risks of initiating treatment without a surgical diagnosis or delaying the discovery of non-endometriosis pathology when determining the appropriate course of management for an individual patient.

6 | RECOMMENDATIONS FOR RESHAPING THE DIAGNOSIS OF ENDOMETRIOSIS

Despite limitations in the knowledge and evidence base regarding endometriosis—from the most basic understanding of disease pathogenesis through to its diagnosis and management—the present clinical need demands that we consider how to optimize the information and approaches available to us so as to provide cost-effective interventions for patients. To that end, we have developed several recommendations to increase the understanding of endometriosis and promote its accurate and timely diagnosis that could be meritorious and worthy of future study.

6.1 | Short-term suggestions

In our opinion, significant advances for patients could be achieved by improving and quantifying the value of nonsurgical diagnosis of symptomatic endometriosis. Our approach to the question of surgical versus clinical diagnosis of symptomatic endometriosis, though informative and based on clinical evidence, should be considered hypothesis-generating. We see the next step in reconciling this query to be a collaboration among professional societies to analyze the data critically and introduce quantitative approaches to diagnosis. This undertaking would involve multiple areas of investigation (Box 1).

At the most rudimentary level, development of an algorithm based on clinical evaluations that could identify patients with the greatest likelihood of endometriosis who are, therefore, candidates for further evaluation would be of considerable value to clinicians, both in primary care and gynecologic practice. A paradigm for early evaluation and diagnosis would be particularly useful to primary care physicians, who are often the first point of contact for patients with symptoms of endometriosis.[61]

BOX 1 Improving Endometriosis Diagnosis: Topics for Future Research and Development

- An assessment of response to first-line therapy (over-the-counter analgesics, NSAIDs, and oral contraceptives) as an indicator of endometriosis. The fundamental question here is whether response, or lack thereof, is indicative of endometriosis. Variables such as complete response, partial response, and the time course of changes in pain and/or other symptoms should be included in the evaluation.
- A quantitative analysis of the contribution of imaging modalities to the diagnosis of endometriosis. The value of both hard and soft markers should be evaluated, and the interobserver reliability of these markers among practitioners assessed.
- Embarking on studies that increase understanding of the risk of disease progression among women with untreated endometriosis. Although a diagnostic delay of 7 years or longer has been well documented,[2,4,5] there are few data to objectively validate the perspective that early accurate diagnosis and initiation of treatment improve long-term outcomes (e.g. fertility, relief of chronic pain, reduced risk of clear cell or endometrioid ovarian carcinoma, and fewer cases of preeclampsia and preterm delivery).[55–58] Nonetheless, expert opinion and clinical experience support the plausibility that early diagnosis will reduce long-term morbidity.[59] The argument for early diagnosis is further strengthened by the observation that advanced-stage disease is more common among young women than has been typically appreciated.[60] To assess the question of the clinical value of early diagnosis in the prevention of endometriosis-related sequelae, data mining can be applied to existing repositories, such as medical insurance claims databases and electronic medical records. However, the most definitive data would be derived from rigorous longitudinal studies.
- Establishing criteria and paradigms for clinical, visual, and histologic diagnosis of endometriosis that consider patient preferences, cost-effectiveness, and ease of implementation in clinical practice.

6.2 | Long-term needs and opportunities

Increased understanding of the natural history of endometriosis as it relates to symptom development and presentation (e.g. pain, menstrual anomalies, gastrointestinal symptoms, fatigue, bloating, and paresthesia) would help clinicians to differentiate endometriosis from other conditions that share symptomology. This type of information is best gleaned through clinical studies that examine patient experiences with symptoms and how they vary with time, age, and menstrual cycle. Comparative data, collected from patient diaries, could be gathered from women with and without endometriosis to determine how the type, frequency, and severity of symptoms differ between these two groups, with further analysis by demographic and

clinical parameters such as current age and symptom history. Studies measuring the response of symptoms to first-line therapies in various patient groups could also prove informative for differential diagnosis (e.g. relief of pain among women with primary dysmenorrhea versus dysmenorrhea due to endometriosis). Nomograms of symptoms could then be developed from these data to illustrate the differences in symptomology among women with endometriosis, women without endometriosis, and women with other gynecologic conditions.

Understanding disease pathogenesis is also a first step to biomarker development. To date, no single biomarker or combination of biomarkers (e.g. endometrial, blood-based, or urinary) has emerged as the standard for diagnosis of endometriosis.[62–65] The lack of a definitive biomarker is not an indictment of those that have been studied, rather it reflects the state of the available evidence, which is constrained by studies with small sample sizes and other methodological limitations. Indeed, we believe that the future of biomarkers is strong, as evidenced by their widespread use in other fields of medicine and the multitude of investigations that have already identified several promising biomarkers for endometriosis.[66–68] Development of biomarkers in the context of endometriosis would be bolstered by well-designed studies that include biomarkers in conjunction with other clinical diagnostic measures. The World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonisation Project is making progress toward enhanced understanding through global research collaboration.[69–72]

7 | CONCLUSION

The present investigation of diagnostic modalities for endometriosis has resulted in several important conclusions. First, there is considerable opportunity to reduce the time to diagnosis for a disease that creates a major quality-of-life burden for many affected individuals. Second, a clinical diagnosis could have distinct value because it is noninvasive and based on simple techniques that are generally routine; available to both primary care and subspecialty clinicians; and can be broadly applied without appreciable alterations to standard practices and patient flow. On a global scale, a simple clinical approach to diagnosis could have wide application in low-resource settings. Indeed, WES recommends that diagnosis of endometriosis in such settings should begin with "two simple questions about pelvic-abdominal pain and infertility".[11] Advancing this idea to include further resource-sparing, but informative, assessments is another step forward in patient care. Third, we have yet to quantify the accuracy of combining biomarkers and other objective indicators of disease with physical examination and imaging findings as constituents of a comprehensive diagnostic paradigm. Fourth, when considered objectively, surgical diagnosis is neither clearly superior nor more accurate than clinical diagnosis, as many clinicians have been taught to believe. Indeed, this perception is a product of focus on a visually or histologically defined lesion as the disease, to the exclusion of the symptomatic presentation. In addition to accuracy, issues of access to care (from an economic and geographic perspective) and surgical risk also must be factored into the paradigm for diagnosis of symptomatic endometriosis. Finally, initiation of endometriosis treatment should not be predicated on a surgical diagnosis. In practice (and in accordance with clinical guidelines), empiric therapy is appropriate for patients whose symptoms and clinical evaluation are consistent with endometriosis (e.g. women with cyclic progressive pelvic pain not attributable to other conditions).

The potential for clinical diagnosis of symptomatic endometriosis does not negate the value of laparoscopy nor does it mean that laparoscopy will not be eventually required for a subset of patients diagnosed clinically. Surgical intervention remains a valuable management option for cases where medical therapy does not provide sufficient symptom relief or when scarring could be present. This approach also allows pathologic and/or histologic validation of the diagnosis. In addition, there are patients for whom laparoscopy could be beneficial before implementation of medical therapy, such as cases where a mass is detected on clinical evaluation, malignancy is suspected, or when the diagnosis is unclear.

Ultimately, regardless of individual opinions or preferences regarding clinical versus surgical diagnosis, our common goal is to accelerate recognition of symptomatic endometriosis so that we can increase access to appropriate and effective management options and reduce the burden of disease.

AUTHOR CONTRIBUTIONS

This manuscript was developed based on the ideation of, and discussions among, HST, GDA, MPD, SRG, AWH, SAM, MCS, ES, and RNT. All authors contributed critical insights, reviewed, critiqued, and provided revisions of the manuscript throughout the development of the article.

ACKNOWLEDGMENTS

Medical writing support for development of this manuscript, funded by AbbVie Inc, was provided by Crystal Murcia and Lamara D Shrode of JB Ashtin.

CONFLICTS OF INTEREST

HST has received research support from OvaScience and Pfizer and has served as a consultant for AbbVie, Bayer, OvaScience, ObsEva, Pfizer, and Therapeutics MD. GDA has ownership in Advanced Reproductive Care Fertility, has consulted for AbbVie, Bayer, Ferring, Guerbet, Hernest, Merck, and Ziva, and is President of the World Endometriosis Research Foundation. MPD owns stock and serves on the Board of Directors of Advanced Reproductive Care, and has received research support from AbbVie, Bayer, and ObsEva. SRG has served as a consultant for Philips Ultrasound, Cooper Surgical, and JDS Therapeutics, and has participated in advisory boards for AbbVie, Allergan, AMAG Pharmaceuticals, Pfizer, Sermonix, Shionogi, and Therapeutics MD. AWH receives research funding from the UK Medical Research Council, National Institute for Health Research, and Wellbeing of Women, and is Chair of the European Society of Human Reproduction and Embryology Special Interest Group on Endometriosis and

Endometrial Disorders. SAM has served as a consultant for AbbVie, and is Secretary for the World Endometriosis Research Foundation and Chair-Elect of the American Society for Reproductive Medicine Endometriosis Special Interest Group. MCS is an employee of AbbVie. ES has received research support, served on medical advisory boards, and has been a member of the speakers' bureau for AbbVie and Ferring. RNT has received research support from Bayer, Ferring, the National Institutes of Health, and Pfizer; has served as a consultant for AbbVie, Actavis, Bayer, ObsEva, and Pfizer; and is the former honorary secretary of the World Endometriosis Society.

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